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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/747,538 | 12/21/2000 | David Aaron Katz | 6652.US.01 | 2085 |

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| EXAMINER | |
|---|---|
| CHUNDURU, SURYAPRABHA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1637 | |

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/747,538 | KATZ ET AL. | |
| | Examiner | Art Unit | |
| | Suryaprabha Chunduru | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *17,18,38-41 and 43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,38-41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

1. Acknowledgement is made for the request to establish continued prosecution application (RCE) filed on February 2, 2005. The request for RCE is accepted and is established with the status of the application as follows: the filling date of this RCE is established as December 21, 2000; Applicants' response to the earlier office action filed along with RCE is considered and has been entered.

### *Status of the Application*

2. The action is in response to the RCE filed on February 2, 2005. Currently claims 17-18, 38-41, and 43 are pending. Claims 1-16, 19-37, and 42 are cancelled. All arguments and amendment have been fully considered and thoroughly reviewed and deemed persuasive in part. The rejections under 35 USC 102(e) are maintained herein because Applicants' arguments are unpersuasive as discussed below. The rejection under 35 USC 103(a) is withdrawn herein in view of the persuasive arguments.

### *New Grounds of Rejections*

### *Claim Rejections - 35 USC § 102*

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

A. Claims 17 and 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer et al. (USPN. 6,232,079).

Wittwer et al. teach a method of claim 17, for monitoring hybridization during PCR for detecting a target nucleic acid sequence in a test sample comprising

(a) contacting the test sample with amplification reagents comprising a polymerase, a PCR primer pair, and a probe (see column 6, lines 1-15, column 44, lines 24-38);

(b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, (ii) lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, (iii and iv) raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to temperature dependent polymerase extension (see column 44, lines 50-67, column 45, lines 1-12 wherein the step of maintaining the reaction mixture for a time and at a temperature sufficient to dissociate the probe hybrid and activating polymerase to a temperature to initiate primer extension occurs simultaneously, see also col.29, line 13-36, col. 35, line 8-31);

(c) repeatedly performing the PCR cycles to form an amplification product (see column 45, lines 13-53) and (d) detection of the amplification product as an indication of presence of the nucleic acid (see column 45, lines 13-53).

With regard to claim 18, Wittwer et al. also disclose that the target nucleic acid sequence is a polymorphic nucleic acid sequence (see column 44, lines 24-38). Thus the disclosure of Wittwer et al. meets the limitations in the instant claims.

B. Claims 38-40, 43 are rejected under 35 U.S.C. 102(b) as being anticipated by Meyer et al. (USPN. 5,648,482).

Meyer teaches a method of claim 38, for determining deletion or insertion (mutant alleles) of at least 50 base pairs in DNA in a test sample comprising:

(a) contacting the test sample with amplification reagents, wherein the amplification reagents comprise amplification primers, to form a reaction mixture in which the amplification primers hybridize with a target nucleic acid sequence (mutant alleles) and a standard nucleic acid sequence (wild-type) in the test sample (see col. 6, line 1-4);

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid amplification product, if the target nucleic acid is present in the test sample (mutant allele- short fragment) and a standard nucleic acid amplification product (wild-type – long product) (see col. 6, line 4-14, line 53-67, col. 7, line 1-7, col. 9, line 13-40);

(c, d) detecting first and second signal that is proportional to the amount of the target and standard nucleic acid amplification product (see col. line 6-20, line 65-67, col. 7, line 1-7, col. 9, line Fig. 9, col. 9, line15-29);

(e) comparing the first signal to second signal to determine whether a deletion or insertion of at least 50 base pairs is present in DNA in the test sample, wherein the amplification reagents comprise one primer that hybridizes to both the target and the standard nucleic acid sequence (see col. 9, line 15-35, wherein SEQ ID No.1 hybridizes to both mutant and wild-type nucleic acid sequence).

With regard to claims 39-40, Meyer teaches that the deletion or insertion (mutant allele) comprises base pairs ranging from at least 200 to 1000 bp (see col. 9, line 15-40).

With regard claim 43, Meyer teaches that the deletion or insertion (mutation) is in the CYP2D6 locus (see col. 9, line 15-40).

Thus the disclosure of Meyer meets the limitations in the instant claims.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 41 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meyer (USPN. 5,648,482) in view of Wittwer et al. (USPN. 6,232,079). .

Meyer teaches a method of claim 38, for determining deletion or insertion (mutant alleles) of at least 50 base pairs in DNA in a test sample comprising:

(a) contacting the test sample with amplification reagents, wherein the amplification reagents comprise amplification primers, to form a reaction mixture in which the amplification primers hybridize with a target nucleic acid sequence (mutant alleles) and a standard nucleic acid sequence (wild-type) in the test sample (see col. 6, line 1-4);

(b) subjecting the reaction mixture to amplification conditions to form a target nucleic acid amplification product, if the target nucleic acid is present in the test sample (mutant allele- short fragment) and a standard nucleic acid amplification product (wild-type – long product) (see col. 6, line 4-14, line 53-67, col. 7, line 1-7, col. 9, line 13-40);

(c, d) detecting first and second signal that is proportional to the amount of the target and standard nucleic acid amplification product (see col. line 6-20, line 65-67, col. 7, line 1-7, col. 9, line Fig. 9, col. 9, line15-29);

(e) comparing the first signal to second signal to determine whether a deletion or insertion of at least 50 base pairs is present in DNA in the test sample, wherein the amplification reagents comprise one primer that hybridizes to both the target and the standard nucleic acid sequence (see col. 9, line 15-35, wherein SEQ ID No.1 hybridizes to both mutant and wild-type nucleic acid sequence). However Meyer did not specifically teach amplification in the presence of a probe using probe-target melting temperatures.

Wittwer et al. teach a method for monitoring hybridization during PCR for detecting a target nucleic acid sequence in a test sample comprising (a) contacting the test sample with amplification reagents comprising a polymerase, a PCR primer pair, and a probe (see column 6, lines 1-15, column 44, lines 24-38); (b) performing PCR cycles (i) raising temperature to dissociate the double-stranded genomic DNA, lowering the temperature to allow primers and probe to hybridize to the target nucleic acid, raising the temperature to dissociate the target-probe hybrids and extending the primers and continuously raising the temperature to temperature dependent polymerase extension (see column 44, lines 50-67, column 45, lines 1-12); (c) repeatedly performing the PCR cycles to form an amplification product (see column 45, lines 13-53) and (d) detection of the amplification product as an indication of presence of the nucleic acid (see column 45, lines 13-53).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made, to combine the method of amplification of a target nucleic acid as taught by Meyer with the step of primer extension in the presence of a probe or monitoring hybridization during PCR as taught by Wittwer et al. to achieve expected advantage of developing a sensitive and enhanced method for amplification of a specific target. An ordinary skill in the art would have reasonable expectation of success that the modification of the method taught by Meyer with the step of monitoring hybridization during PCR would result in continuously monitoring of DNA amplification, identification and quantitation of the target nucleic acid and reducing laborious processing steps after PCR to identify the said target nucleic acid (see col. 3, line 14-33). Therefore an ordinary practitioner would have been motivated to combine the method of Meyer with the inclusion of step of monitoring hybridization during PCR

as taught by Wittwer et al. to develop a sensitive and enhanced method for amplification and quantitation of a specific target nucleic acid.

***Response to arguments***

5. With regard to the rejection made in the previous office action under 35 USC 102(e) over Wittwer et al., Applicants' arguments and amendment have been fully considered and found unpersuasive. Applicants' argue that Wittwer et al. did not teach four –step temperature cycle and argue that the disclosure of Wittwer et al. does not work for relative qunatitation of target sequences by substantially eliminating the noise related to cross-hybridization prior to signal detection as disclosed in the instant invention. Applicants' arguments are fully considered and found unpersuasive for two reasons. First, Wittwer et al. teach the four temperature steps as claimed in the instant claims. The disclosure of Wittwer et al. the step of maintaining the reaction mixture for a time and at a temperature sufficient to dissociate the probe hybrid and activating polymerase to a temperature to initiate primer extension occurring simultaneously. Since the claims are in 'comprising' format any additional steps are permissible. Thus the disclosure of Wittwer et al. does not exclude the steps as claimed in the instant claims and Wittwer et al. does teach quantitation of target nucleic acid sequences by monitoring and measuring fluorescence signals during PCR amplification. Second, As noted in MPEP 2145 "Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993)", the limitation 'relative quantitation by substantially eliminating the noise related to cross-hybridization prior to signal detection' upon which the arguments are based, is *not* present in the claims. Therefore the

disclosure of Wittwer et al. does anticipate the instant claims and the rejection is maintained and rewritten as above.

6. With regard to the rejection made in the previous office action under 35 USC 102(e) over Lapidus et al., Applicants' arguments and amendment are fully considered and the rejection is withdrawn in view of persuasive arguments and new grounds of rejections.

7. With regard to the rejection maintained in the previous office action under 35 USC 103(a), Applicants' arguments are fully considered and the rejection is withdrawn in view of persuasive arguments and new grounds of rejections.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M , Mon - Friday,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suryaprabha Chunduru
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
2/15/05